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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	May 10	PROUSDDR now available on STN
NEWS 4	May 19	PROUSDDR: One FREE connect hour, per account, in both May and June 2004
NEWS 5	May 12	EXTEND option available in structure searching
NEWS 6	May 12	Polymer links for the POLYLINK command completed in REGISTRY
NEWS 7	May 17	FRFULL now available on STN
NEWS 8	May 27	New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus
NEWS 9	May 27	CAplus super roles and document types searchable in REGISTRY
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NEWS 11	Jun 22	STN Patent Forums to be held July 19-22, 2004

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:55:16 ON 23 JUN 2004

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 12:55:42 ON 23 JUN 2004
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 22 JUN 2004 HIGHEST RN 697737-72-7
DICTIONARY FILE UPDATES: 22 JUN 2004 HIGHEST RN 697737-72-7

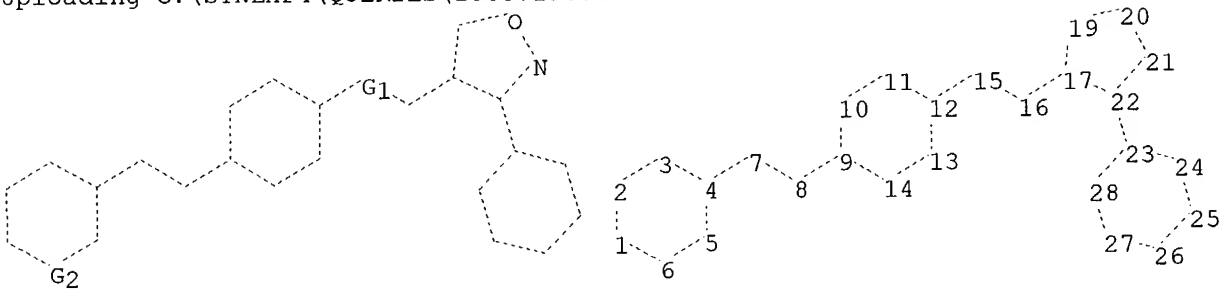
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\STNEXP4\QUERIES\10637190.str



chain nodes :
7 8 15 16
ring nodes :
1 2 3 4 5 6 9 10 11 12 13 14 17 19 20 21 22 23 24 25 26 27 28

chain bonds :
4-7 7-8 8-9 12-15 15-16 16-17 22-23
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14 17-19 17-22
19-20 20-21 21-22 23-24 23-28 24-25 25-26 26-27 27-28
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 4-7 5-6 7-8 8-9 9-10 9-14 10-11 11-12 12-13 12-15
13-14 15-16 16-17 17-19 17-22 19-20 20-21 21-22 22-23 23-24 23-28 24-25
25-26 26-27 27-28

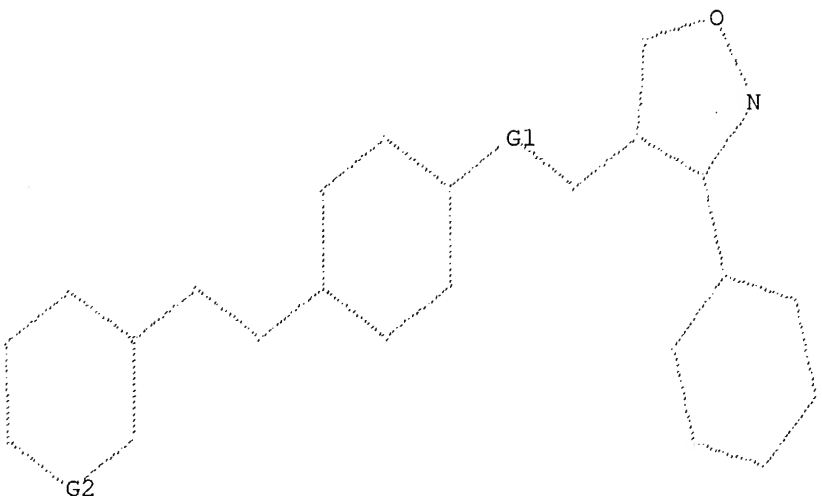
G1:O,N

G2:C,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:Atom 19:Atom 20:Atom
21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 O,N

G2 C,N

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 1 TO ITERATE

100.0% PROCESSED 1 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1 TO 80
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> s l1 full
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FULL SCREEN SEARCH COMPLETED - 21 TO ITERATE

100.0% PROCESSED 21 ITERATIONS 15 ANSWERS
SEARCH TIME: 00.00.01

L3 15 SEA SSS FUL L1

=> s l3 and caplus/lc
35942085 CAPLUS/LC
L4 10 L3 AND CAPLUS/LC

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=> s l3 not l4
L5              5 L3 NOT L4

=> d l5 1-5
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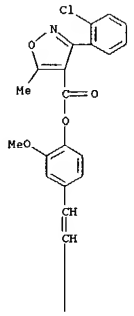
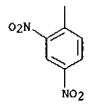
L5 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 463316-13-4 REGISTRY
CN 4-Isoxazolecarboxylic acid, 3-(2-chlorophenyl)-5-methyl-, 4-[2-(2,4-dinitrophenyl)ethenyl]-2-methoxyphenyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H18 Cl N3 O8
SR Chemical Library
LC STN Files: CHEMCATS

PAGE 1-A



PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L5 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 462624-31-3 REGISTRY
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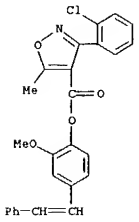
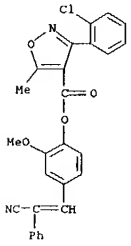
FS 3D CONCORD
MF C26 H20 Cl N O4
SR Chemical Library
LC STN Files: CHEMCATS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

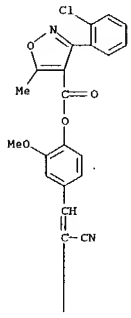
L5 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 462611-49-0 REGISTRY
CN 4-Isoxazolecarboxylic acid, 3-(2-chlorophenyl)-5-methyl-, 4-(2-cyano-2-phenylethenyl)-2-methoxyphenyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H19 Cl N2 O4
SR Chemical Library
LC STN Files: CHEMCATS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L5 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 302574-97-6 REGISTRY
CN 4-Isoxazolecarboxylic acid, 3-(2-chlorophenyl)-5-methyl-, 4-[2-(4-chlorophenyl)-2-cyanoethenyl]-2-methoxyphenyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H18 Cl2 N2 O4
SR Chemical Library
LC STN Files: CHEMCATS

PAGE 1-A



PAGE 2-A

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L5 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 219865-50-6 REGISTRY
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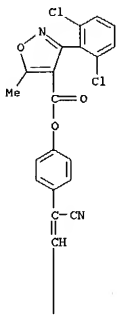
FS 3D CONCORD
MF C27 H15 Cl2 F3 N2 O3
SR CAS Client Services
LC STN Files: CHEMCATS

PAGE 1-A



PAGE 2-A

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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=> fil caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       172.06     172.27

FILE 'CAPLUS' ENTERED AT 13:01:18 ON 23 JUN 2004
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FILE COVERS 1907 - 23 Jun 2004  VOL 140 ISS 26
FILE LAST UPDATED: 22 Jun 2004  (20040622/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> d his

     (FILE 'HOME' ENTERED AT 12:55:16 ON 23 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 12:55:42 ON 23 JUN 2004
L1                STRUCTURE UPLOADED
L2              1 S L1
L3             15 S L1 FULL
L4             10 S L3 AND CAPLUS/LC
L5              5 S L3 NOT L4

     FILE 'CAPLUS' ENTERED AT 13:01:18 ON 23 JUN 2004

=> s l4
L6             19 L4

=> s l4 and Farnesoid
             19 L4
            253 FARNESOID
              3 FARNESOIDS
            255 FARNESOID
                  (FARNESOID OR FARNESOIDS)
L7             16 L4 AND FARNESOID

=> d ibib abs hitstr 1016
     16 ANSWERS ARE AVAILABLE.  SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1):1-16
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L7 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:453343 CAPLUS
TITLE: Crystal structure of the human **farnesoid** X receptor ligand binding domain complexed with fexaramine and identification and development of novel small molecule ligands for FXR
INVENTOR(S): Downes, Michael R.; Verdicia, Mark A.; Noel, Joseph P.; Evans, Ronald M.; Bowman, Lindsey J.; Bowman, Marianne
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004046323	A2	20040603	WO 2003-US36548	20031114

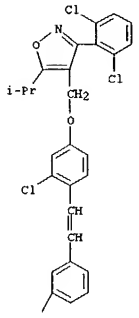
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-426665P P 20021115
US 2002-426668P P 20021115

AB The present invention provides compns. comprising the ligand binding domain (LBD) of a human **farnesoid** X receptor (FXR) in crystalline form. In alternative embodiments, the LBD of FXR is complexed with a ligand therefor. There are provided high resolution structures and structure coordinates of FXR complexed with a novel high affinity agonist, fexaramine. The discovered structure of a FXR LBD provides the first three-dimensional view of the structural basis for FXR ligand binding. The present invention further provides a computer for producing a three-dimensional representation of FXR or a complex thereof, and a computer for determining at least a portion of the structure coordinates of FXR or a complex thereof. The present invention further provides methods of using this structural information to predict mols. capable of binding to FXR; to identify compds. with agonist, antagonist or partial agonist activity for FXR; and to determine whether a test compound is capable of binding to the LBD of FXR. The present invention further provides compns. comprising compds. identified by such invention methods. Identification and development of novel small mol. ligands for FXR, and activation of FXR and induction of FXR target genes by these novel compds. is disclosed.

IT INDEXING IN PROGRESS
IT **278779-30-9P**, GW4064
RL: BSU (Biological study, unclassified); CPN (Combinatorial preparation);
THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(FXR ligand; crystal structure of human **farnesoid** X receptor ligand binding domain complexed with fexaramine and identification and development of novel small mol. ligands for FXR)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L7 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:453231 CAPLUS
TITLE: Non-steroidal fxr agonists
INVENTOR(S): Nicolaou, Kyriacos C.; Roecker, Anthony J.; Hughes, Robert; Pfefferkorn, Jeffrey A.
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004046162	A2	20040603	WO 2003-US36195	20031114

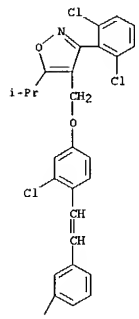
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-426456P P 20021114
US 2003-491185P P 20030729

AB Abstract Potent non-steroidal **farnesoid** X receptor (FXR) agonists are N-aryl-N-arylmethyl amido and ureido compds. having the chemical structure represented by the following formula (I): INSERT FORMULA wherein E1 is (C1-C8)alkyl, cyclohexyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, Ph, or NH(C1-C8)alkyl; L1 and L2 are both H, or together form a pi-bond; X1 is C(O), or CH2; Y1 is H, NHZ1, NH(Z2)Z3, or OZ4; aryl moiety A1 is selected from the group of radicals consisting of: INSERT FORMULA A2 and G1 - G11 are as defined in the specification; and T1 and T2 are each independently O, S, NH, or N(C1-C8)alkyl. The FXR agonists are useful as therapeutic agents for the treatment of diseases linked to cholesterol, bile acids, and their metabolism and homeostasis.

IT INDEXING IN PROGRESS
IT **278779-30-9**, GW 4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-steroidal fxr agonists)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L7 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:973413 CAPLUS
DOCUMENT NUMBER: 140:229012
TITLE: Hepatoprotection by the **farnesoid** X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis
AUTHOR(S): Liu, Yaping; Binz, Jane; Numerick, Mary Jo; Dennis, Steve; Luo, Guizhen; Desai, Bhasha; MacKenzie, Kathleen I.; Mansfield, Traci A.; Kliewer, Steven A.; Goodwin, Bryan; Jones, Stacey A.
CORPORATE SOURCE: Nuclear Receptor Functional Analysis, High Throughput Biology, GlaxoSmithKline, Research Triangle Park, NC, USA
SOURCE: Journal of Clinical Investigation (2003), 112(11), 1678-1687
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

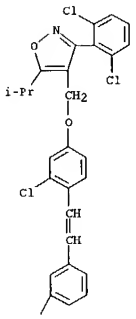
AB **Farnesoid** X receptor (FXR) is a bile acid-activated transcription factor that is a member of the nuclear hormone receptor superfamily. Fxr-null mice exhibit a phenotype similar to Byler disease, an inherited cholestatic liver disorder. In the liver, activation of FXR induces transcription of transporter genes involved in promoting bile acid clearance and represses genes involved in bile acid biosynthesis. We investigated whether the synthetic FXR agonist GW4064 could protect against cholestatic liver damage in rat models of extrahepatic and intrahepatic cholestasis. In the bile duct-ligation and α-naphthylisothiocyanate models of cholestasis, GW4064 treatment resulted in significant redns. in serum alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase, as well as other markers of liver damage. Rats that received GW4064 treatment also had decreased incidence and extent of necrosis, decreased inflammatory cell infiltration, and decreased bile duct proliferation. Anal. of gene expression in livers from GW4064-treated cholestatic rats revealed decreased expression of bile acid biosynthetic genes and increased expression of genes involved in bile acid transport, including the phospholipid flippase MDR2. The hepatoprotection seen in these animal models by the synthetic FXR agonist suggests FXR agonists may be useful in the treatment of cholestatic liver disease.

IT **278779-30-9**, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hepatoprotection by **farnesoid** X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:855658 CAPLUS
DOCUMENT NUMBER: 139:317457
TITLE: Compositions and methods using **farnesoid** X receptor ligands for hepatoprotection and treatment of cholestasis
INVENTOR(S): Kliewer, Steven Anthony; Willson, Timothy Mark
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003203939	A1	20031030	US 2002-132311	20020425
WO 2003090745	A1	20031106	WO 2003-US10519	20030407

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-132311 A 20020425
OTHER SOURCE(S): MARPAT 139:317457

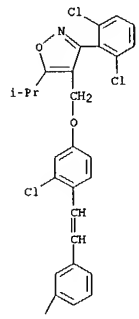
AB Methods for the treatment of cholestatic liver disease and reduction and prevention of hepatic injury resulting from cholestasis via administration of a FXR ligand are provided. Bile duct-ligated rats treated with FXR ligand GW4064 had a pronounced improvement in liver function as defined by a reduction in a panel of liver disease serum marker enzymes.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(FXR agonist; **farnesoid** X receptor ligands for hepatoprotection and treatment of cholestasis)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

L7 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:777952 CAPLUS
DOCUMENT NUMBER: 139:286360
TITLE: Methods using **farnesoid** X receptor (FXR) agonists for weight loss and alteration of cell metabolism
INVENTOR(S): Jones, Stacey Ann; Kliewer, Steven Anthony; Mansfield, Traci Ann
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Curagen Corporation
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080803	A2	20031002	WO 2003-US8634	20030319

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-366463P P 20020321
OTHER SOURCE(S): MARPAT 139:286360

AB Treatment of human hepatocytes with **farnesoid** X receptor (FXR) agonists resulted in increased expression of FGF-19. Methods of using FXR agonists to alter cell metabolism, and in pharmaceutical weight loss methods, are described.

IT **278779-30-9**, GW4064 **278779-30-9D**, GW4064, amino acid conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**farnesoid** X receptor agonists for weight loss and alteration of cell metabolism)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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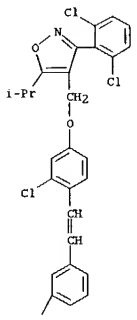

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L7 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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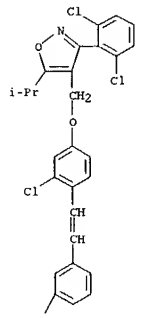

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RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:723027 CAPLUS
DOCUMENT NUMBER: 139:286515
TITLE: Estrogen receptor α regulates expression of the orphan receptor small heterodimer partner
AUTHOR(S): Lai, KehDih; Harnish, Douglas C.; Evans, Mark J.
CORPORATE SOURCE: Wyeth Research, Collegeville, PA, 19426, USA
SOURCE: Journal of Biological Chemistry (2003), 278(38), 36418-36429
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hormonal status can influence diverse metabolic pathways. Small heterodimer partner (SHP) is an orphan nuclear receptor that can modulate the activity of several transcription factors. Estrogens are here shown to directly induce expression of the SHP in the mouse and rat liver and in human HepG2 cells. SHP is rapidly induced within 2 h following treatment of mice with ethynylestradiol (EE) or the estrogen receptor α (ERα)-selective compound Pr pyrazole triol (PPT). SHP induction by these estrogens is completely absent in ERαKO mice. Mutation of the human SHP promoter defined HNF-3, HNF-4, GATA, and AP-1 sites as important for basal activity, whereas EE induction required two distinct elements located between -309 and -267. One of these elements contains an estrogen response element half-site that bound purified ERα, and ERα with a mutated DNA binding domain was unable to stimulate SHP promoter activity. This ERα binding site overlaps the known **farnesoid** X receptor (FXR) binding site in the SHP promoter, and the combination of EE plus FXR agonists did not produce an additive induction of SHP expression in mice. Surprisingly, induction of SHP by EE did not inhibit expression of the known SHP target genes cholesterol 7α-hydroxylase (CYP7A1) or sterol 12α-hydroxylase (CYP8B1). However, the direct regulation of SHP expression may provide a basis for some of the numerous biol. effects of estrogens.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(estrogen receptor α regulates expression of orphan receptor small heterodimer partner as studied in mouse and rat liver and in human HepG2 cells)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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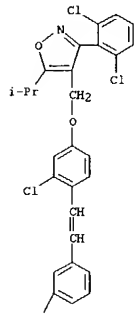

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REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:698404 CAPLUS
DOCUMENT NUMBER: 140:87450
TITLE: **Farnesoid** X receptor agonists suppress hepatic apolipoprotein CIII expression
AUTHOR(S): Claudel, Thierry; Inoue, Yusuke; Barbier, Olivier; Duran-Sandoval, Daniel; Kosykh, Vladimir; Fruchart, Jamila; Fruchart, Jean-Charles; Gonzalez, Frank J.; Staels, Bart
CORPORATE SOURCE: Departement d'Atherosclerose, UR545 INSERM, Institut Pasteur de Lille, Lille, Fr.
SOURCE: Gastroenterology (2003), 125(2), 544-555
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background & Aims: Increased serum triglyceride levels constitute a risk factor for coronary heart disease. Apolipoprotein CIII (Apo CIII) is a determinant of serum triglyceride metabolism In this study, we investigated whether activators of the nuclear **farnesoid** X receptor (FXR) modulate Apo CIII gene expression. Methods: The influence of bile acids and synthetic FXR activators on Apo CIII and triglyceride metabolism was studied in vivo by using FXR wild-type and FXR-deficient mice and in vitro by using human primary hepatocytes and HepG2 cells. Results: In mice, treatment with the FXR agonist taurocholic acid strongly decreased serum triglyceride levels, an effect associated with reduced Apo CIII serum and liver mRNA levels. By contrast, no change was observed in FXR-deficient mice. Incubation of human primary hepatocytes and HepG2 cells with bile acids or the nonsteroidal synthetic FXR agonist GW4064 resulted in a dose-dependent downregulation of Apo CIII gene expression. Promoter transfection expts. and mutation anal. showed that bile acid-activated FXR decrease human Apo CIII promoter activity via a neg. FXR response element located in the 14 footprint between nucleotides -739 and -704. Chromatin immunopptn. expts. showed that bile acid treatment led to binding of FXR/retinoid X receptor heterodimers to and displacement of HNF4α from this site. Bile acid treatment still repressed liver Apo CIII gene expression in hepatic HNF4α-deficient mice, suggesting an active rather than a competitive mechanism of Apo CIII repression by the FXR. Conclusions: We identified bile acid and synthetic activators of the nuclear FXR as neg. regulators of Apo CIII expression, an effect that may contribute to the triglyceride-decreasing action of FXR agonists.

IT **278779-30-9**, GW4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**farnesoid** X receptor agonists suppress hepatic apolipoprotein CIII expression)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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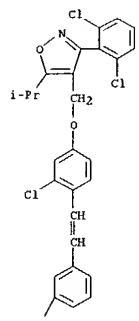

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REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:579493 CAPLUS
DOCUMENT NUMBER: 139:256039
TITLE: Human kininogen gene is transactivated by the **farnesoid** X receptor
AUTHOR(S): Zhao, Annie; Lew, Jane-L.; Huang, Li; Yu, Jinghua; Zhang, Theresa; Hrywna, Yaroslav; Thompson, John R.; de Pedro, Nuria; Blevins, Richard A.; Pelaez, Fernando; Wright, Samuel D.; Cui, Jisong
CORPORATE SOURCE: Departments of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2003), 278(31), 28765-28770
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human kininogen belongs to the plasma kallikrein-kinin system. High mol. weight kininogen is the precursor for two-chain kinin-free kininogen and bradykinin. It has been shown that the two-chain kinin-free kininogen has the properties of anti-adhesion, anti-platelet aggregation, and anti-thrombosis, whereas bradykinin is a potent vasodilator and mediator of inflammation. In this study the human kininogen gene is strongly up-regulated by agonists of the **farnesoid** X receptor (FXR), a nuclear receptor for bile acids. In primary human hepatocytes, both the endogenous FXR agonist chenodeoxycholate and synthetic FXR agonist GW4064 increased kininogen mRNA with a maximum induction of 8-10-fold. A more robust induction of kininogen expression was observed in HepG2 cells, where kininogen mRNA was increased by chenodeoxycholate or GW4064 up to 130-140-fold as shown by real time PCR. Northern blot anal. confirmed the up-regulation of kininogen expression by FXR agonists. To determine whether kininogen is a direct target of FXR, the authors examined the sequence of the kininogen promoter and identified a highly conserved FXR response element (inverted repeat, IR-1) in the proximity of the kininogen promoter (-66/-54). FXR/RXRα heterodimers specifically bind to this IR-1. A construct of a minimal promoter with the luciferase reporter containing this IR-1 was transactivated by FXR. Deletion or mutation of this IR-1 abolished FXR-mediated promoter activation, indicating that this IR-1 element is responsible for the promoter transactivation by FXR. The authors conclude that kininogen is a novel and direct target of FXR, and bile acids may play a role in the vasodilation and anti-coagulation processes.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human kininogen gene is transactivated by the **farnesoid** X receptor in primary human hepatocytes)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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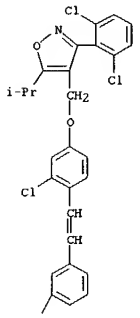

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REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:375244 CAPLUS
DOCUMENT NUMBER: 139:159454
TITLE: A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR
AUTHOR(S): Downes, Michael; Verdecia, Mark A.; Roecker, A. J.; Hughes, Robert; Hogenesch, John B.; Kast-Woelbern, Heidi R.; Bowman, Marianne E.; Ferrer, Jean-Luc; Anisfeld, Andrew M.; Edwards, Peter A.; Rosenfeld, John M.; Alvarez, Jacqueline G. A.; Noel, Joseph P.; Nicolaou, K. C.; Evans, Ronald M.
CORPORATE SOURCE: Gene Expression Laboratory, Howard Hughes Medical Institute, La Jolla, CA, 92037, USA
SOURCE: Molecular Cell (2003), 11(4), 1079-1092
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **farnesoid** X receptor (FXR) functions as a bile acid (BA) sensor coordinating cholesterol metabolism, lipid homeostasis, and absorption of dietary fats and vitamins. However, BAs are poor reagents for characterizing FXR functions due to multiple receptor independent properties. Accordingly, using combinatorial chemical we evolved a small mol. agonist termed fexaramine with 100-fold increased affinity relative to natural compds. Gene-profiling expts. conducted in hepatocytes with FXR-specific fexaramine vs. the primary BA chenodeoxycholic acid (CDCA) produced remarkably distinct genomic targets. Highly diffracting cocrystals (1.78 Å) of fexaramine bound to the ligand binding domain of FXR revealed the agonist sequestered in a 726 Å3 hydrophobic cavity and suggest a mechanistic basis for the initial step in the BA signaling pathway. The discovery of fexaramine will allow us to unravel the FXR genetic network from the BA network and selectively manipulate components of the cholesterol pathway that may be useful in treating cholesterol-related human diseases.

IT **278779-30-9**, GW 4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chemical, genetic, and structural anal. of nuclear bile acid receptor FXR)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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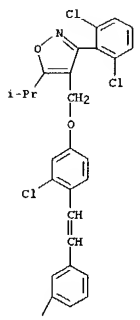

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REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:237176 CAPLUS
DOCUMENT NUMBER: 139:17879
TITLE: Differential regulation of rat and human CYP7A1 by the nuclear oxysterol receptor liver X receptor-α
AUTHOR(S): Goodwin, Bryan; Watson, Michael A.; Kim, Hwajin; Miao, Ji; Kemper, Jongsook Kim; Kliewer, Steven A.
CORPORATE SOURCE: Nuclear Receptor Discovery Research, GlaxoSmithKline Research and Development, Research Triangle Park, NC, 27709, USA
SOURCE: Molecular Endocrinology (2003), 17(3), 386-394
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In rodent liver, transcription of the gene encoding cholesterol 7α-hydroxylase (CYP7A1), which catalyzes the rate-limiting step in the classic bile acid synthetic pathway, is stimulated by the liver X receptor α (LXRα), a nuclear receptor for oxysterol metabolites of cholesterol. This feed-forward regulatory loop provides a mechanism for the elimination of excess cholesterol from the body. The authors demonstrate that in primary cultures of human hepatocytes, activation of LXRα has the opposite effect, repressing CYP7A1 expression. This repression is mediated, at least in part, through induction of the orphan nuclear receptor, short heterodimer partner (SHP), which is also induced by bile acids. The authors demonstrate that SHP is regulated directly by LXRα through a DNA response element that overlaps with the previously characterized bile acid response element. The authors' data reveal a fundamental difference in the regulation of CYP7A1 in rodent and human hepatocytes and provide evidence that different species employ distinct mol. strategies to regulate cholesterol homeostasis.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(differential regulation of rat and human CYP7A1 by nuclear oxysterol receptor liver X receptor-α)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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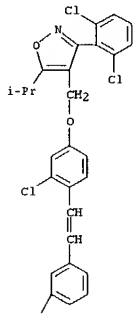

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REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:204786 CAPLUS
DOCUMENT NUMBER: 139:79298
TITLE: Guggulsterone Is a **Farnesoid** X Receptor Antagonist in Coactivator Association Assays but Acts to Enhance Transcription of Bile Salt Export Pump
AUTHOR(S): Cui, Jisong; Huang, Li; Zhao, Annie; Lew, Jane-L.; Yu, Jinghua; Sahoo, Soumya; Meinke, Peter T.; Royo, Inmaculada; Pelaez, Fernando; Wright, Samuel D.
CORPORATE SOURCE: Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2003), 278(12), 10214-10220
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Guggulipid is an extract of the guggul tree Commiphora mukul and has been widely used to treat hyperlipidemia in humans. The plant sterol guggulsterone (GS) is the active agent in this extract Recent studies have shown that GS can act as an antagonist ligand for **farnesoid** X receptor (FXR) and decrease expression of bile acid-activated genes. Here we show that GS, although an FXR antagonist in coactivator association assays, enhances FXR agonist-induced transcription of bile salt export pump (BSEP), a major hepatic bile acid transporter. In HepG2 cells, in the presence of an FXR agonist such as chenodeoxycholate or GW4064, GS enhanced endogenous BSEP expression with a maximum induction of 400-500% that induced by an FXR agonist alone. This enhancement was also readily observed in FXR-dependent BSEP promoter activation using a luciferase reporter construct. In addition, GS alone slightly increased BSEP promoter activation in the absence of an FXR agonist. Consistent with the results in HepG2, guggulipid treatment in Fisher rats increased BSEP mRNA. Interestingly, in these animals expression of the orphan nuclear receptor SHP (small heterodimer partner), a known FXR target, was also significantly increased, whereas expression of other FXR targets including cholesterol 7α-hydroxylase (Cyp 7a1), sterol 12α-hydroxylase (Cyp 8b1), and the intestinal bile acid-binding protein (I-BABP), remained unchanged. Thus, we propose that GS is a selective bile acid receptor modulator that regulates expression of a subset of FXR targets. Guggulipid treatment in rats lowered serum triglyceride and raised serum high d. lipoprotein levels. Taken together, these data suggest that guggulsterone defines a novel class of FXR ligands characterized by antagonist activities in coactivator association assays but with the ability to enhance the action of agonists on BSEP expression in vivo.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FXR agonist; guggulsterone is a **farnesoid** X receptor antagonist in coactivator association assays but Acts to enhance transcription of bile salt export pump)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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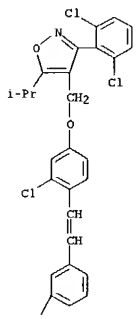

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REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:112477 CAPLUS
DOCUMENT NUMBER: 138:298694
TITLE: Bile acids induce the expression of the human peroxisome proliferator-activated receptor α gene via activation of the **farnesoid** X receptor
AUTHOR(S): Torra, Ines Pineda; Claudel, Thierry; Duval, Caroline; Kosykh, Vladimir; Fruchart, Jean-Charles; Staels, Bart
CORPORATE SOURCE: U.545 Institut National de la Sante et de la Recherche Medicale, Departement d'Atherosclerose, Institut Pasteur de Lille, Lille, 59019, Fr.
SOURCE: Molecular Endocrinology (2003), 17(2), 259-272
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor that controls lipid and glucose metabolism and exerts antiinflammatory activities. PPARα is also reported to influence bile acid formation and bile composition **Farnesoid** X receptor (FXR) is a bile acid-activated nuclear receptor that mediates the effects of bile acids on gene expression and plays a major role in bile acid and possibly also in lipid metabolism Thus, both PPARα and FXR appear to act on common metabolic pathways. To determine the existence of a mol. cross-talk between these two nuclear receptors, the regulation of PPARα expression by bile acids was investigated. Incubation of human hepatoma HepG2 cells with the natural FXR ligand chenodeoxycholic acid (CDCA) as well as with the nonsteroidal FXR agonist GW4064 resulted in a significant induction of PPARα mRNA levels. In addition, hPPARα gene expression was up-regulated by taurocholic acid in human primary hepatocytes. Cotransfection of FXR/retinoid X receptor in the presence of CDCA led to up to a 3-fold induction of human PPARα promoter activity in HepG2 cells. Mutation anal. identified a FXR response element in the human PPARα promoter (α-FXR response element (αFXRE)) that mediates bile acid regulation of this promoter. FXR bound the αFXRE site as demonstrated by gel shift anal., and CDCA specifically increased the activity of a heterologous promoter driven by four copies of the αFXRE. In contrast, neither the murine PPARα promoter, in which the αFXRE is not conserved, nor a mouse αFXRE-driven heterologous reporter, were responsive to CDCA treatment. Moreover, PPARα expression was not regulated in taurocholic acid-fed mice. Finally, induction of hPPARα mRNA levels by CDCA resulted in an enhanced induction of the expression of the PPARα target gene carnitine palmitoyltransferase I by PPARα ligands. In concert, these results demonstrate that bile acids stimulate PPARα expression in a species-specific manner via a FXRE located within the human PPARα promoter. These results provide mol. evidence for a cross-talk between the FXR and PPARα pathways in humans.

IT **278779-30-9**, GW4064
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(PPARα mRNA induction by; bile acids induce the expression of the human peroxisome proliferator-activated receptor α gene via activation of the **farnesoid** X receptor)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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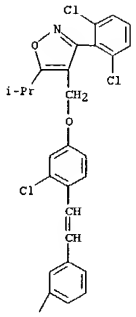

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REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:677926 CAPLUS
DOCUMENT NUMBER: 138:49877
TITLE: Lithocholic acid decreases expression of bile salt export pump through **farnesoid** X receptor antagonist activity
AUTHOR(S): Yu, Jinghua; Lo, Jane-L.; Huang, Li; Zhao, Annie; Metzger, Edward; Adams, Alan; Meinke, Peter T.; Wright, Samuel D.; Cui, Jisong
CORPORATE SOURCE: Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2002), 277(35), 31441-31447
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bile salt export pump (BSEP) is a major bile acid transporter in the liver. Mutations in BSEP result in progressive intrahepatic cholestasis, a severe liver disease that impairs bile flow and causes irreversible liver damage. BSEP is a target for inhibition and down-regulation by drugs and abnormal bile salt metabolites, and such inhibition and down-regulation may result in bile acid retention and intrahepatic cholestasis. In this study, we quant. analyzed the regulation of BSEP expression by FXR ligands in primary human hepatocytes and HepG2 cells. We demonstrate that BSEP expression is dramatically regulated by ligands of the nuclear receptor **farnesoid** X receptor (FXR). Both the endogenous FXR agonist chenodeoxycholate (CDCA) and synthetic FXR ligand GW4064 effectively increased BSEP mRNA in both cell types. This up-regulation was readily detectable at as early as 3 h, and the ligand potency for BSEP regulation correlates with the intrinsic activity on FXR. These results suggest BSEP as a direct target of FXR and support the recent report that the BSEP promoter is transactivated by FXR. In contrast to CDCA and GW4064, lithocholate (LCA), a hydrophobic bile acid and a potent inducer of cholestasis, strongly decreased BSEP expression. Previous studies did not identify LCA as an FXR antagonist ligand in cells, but we show here that LCA is an FXR antagonist with partial agonist activity in cells. In an in vitro coactivator association assay, LCA decreased CDCA- and GW4064-induced FXR activation with an IC50 of 1 μM. In HepG2 cells, LCA also effectively antagonized GW4064-enhanced FXR transactivation. These data suggest that the toxic and cholestat effect of LCA in animals may result from its down-regulation of BSEP through FXR. Taken together, these observations indicate that FXR plays an important role in BSEP gene expression and that FXR ligands may be potential therapeutic drugs for intrahepatic cholestasis.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endogenous FXR agonist chenodeoxycholate and synthetic FXR ligand GW4064 effectively increases BSEP (bile salt export pump) mRNA in primary human hepatocytes and HepG2 cells)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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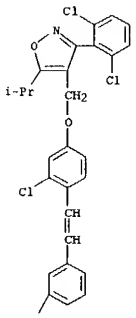

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REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:540315 CAPLUS
DOCUMENT NUMBER: 137:263227
TITLE: 6α-Ethyl-Chenodeoxycholic Acid (6-ECDCA), a Potent and Selective FXR Agonist Endowed with Anticholestatic Activity
AUTHOR(S): Pellicciari, Roberto; Fiorucci, Stefano; Camaioni, Emidio; Clerici, Carlo; Costantino, Gabriele; Maloney, Patrick R.; Morelli, Antonio; Parks, Derek J.; Willson, Timothy M.
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologia del Farmaco, Universita di Perugia, Perugia, 06123, Italy
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3569-3572
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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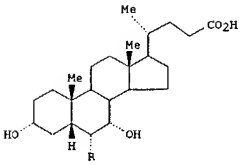


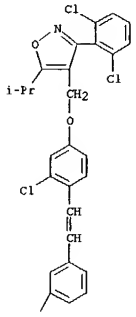
I

AB A series of 6α-alkyl-substituted analogs I (R = Me, Et, Pr, Bn) of chenodeoxycholic acid (CDCA) were synthesized and evaluated as potential **farnesoid** X receptor (FXR) ligands. Among them, 6α-ethyl-chenodeoxycholic acid (6-ECDCA) I (R = Et) was shown to be a very potent and selective FXR agonist (EC50 = 99 nM) and to be endowed with anticholeretic activity in an in vivo rat model of cholestasis.

IT **278779-30-9**, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GW 4064; binding potency to **farnesoid** X receptor agonist endowed with anticholestatic activity)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



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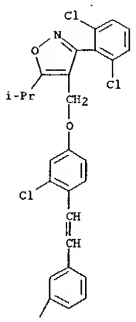
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



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REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:729132 CAPLUS
DOCUMENT NUMBER: 136:18310
TITLE: **Farnesoid** X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids
AUTHOR(S): Kast, Heidi Rachelle; Nguyen, Catherine M.; Sinal, Christopher J.; Jones, Stacey A.; Laffitte, Bryan A.; Reue, Karen; Gonzalez, Frank J.; Willson, Timothy M.; Edwards, Peter A.
CORPORATE SOURCE: Departments of Biological Chemistry and Medicine, University of California, Los Angeles, CA, 90095, USA
SOURCE: Molecular Endocrinology (2001), 15(10), 1720-1728
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **farnesoid** X-activated receptor (FXR; NR1H4), a member of the nuclear hormone receptor superfamily, induces gene expression in response to several bile acids, including chenodeoxycholic acid. Here the authors used suppression subtractive hybridization to identify apolipoprotein C-II (apoC-II) as an FXR target gene. Retroviral expression of FXR in HepG2 cells results in induction of the mRNA encoding apoC-II in response to several FXR ligands. EMSAs demonstrate that recombinant FXR and RXR bind to two FXR response elements that are contained within two important distal enhancer elements (hepatic control regions) that lie 11 kb and 22 kb upstream of the transcription start site of the apoC-II gene. A luciferase reporter gene containing the hepatic control region or two copies of the wild-type FXR response element was activated when FXR-containing cells were treated with FXR ligands. In addition, the authors report that hepatic expression of both apoC-II and phospholipid transfer protein mRNAs increases when mice are fed diets supplemented with cholic acid, an FXR ligand, and this induction is attenuated in FXR null mice. Finally, the authors observed decreased plasma triglyceride levels in mice fed cholic acid- containing diets. These results identify a mechanism whereby FXR and its ligands lower plasma triglyceride levels. These findings may have important implications in the clin. management of hyperlipidemias.

IT **278779-30-9**, GW 4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(**farnesoid** X-activated receptor induces apolipoprotein C-II transcription in HepG2 cells in relation to mol. mechanism linking plasma triglyceride levels to bile acids)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L7 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:441628 CAPLUS
DOCUMENT NUMBER: 133:68969
TITLE: Assays for ligands for nuclear receptors using peptide sequences
INVENTOR(S): Blanchard, Steven Gerard; Kliewer, Anthony; Lehmann, Jurgen; Parks, Derek J.; Stimmel, Julie Beth; Willson, Timothy Mark
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037077	A1	20000629	WO 1999-US30947	19991222
W: AE, AL, AM, AT, AU, AZ, BG, BR, CA, CH, CN, CU, DE, DK, EE, ES, FI, GB, GD, GH, HR, IN, IS, JP, LK, LU, LV, MD, MN, MW, MX, NO, RU, SD, SE				
RW: GH, GM, KE, LS, MW, SD, SL, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, MR, NE, TD, TG				
CA 2356887	AA	20000629	CA 1999-2356887	19991222
EP 1140079	A1	20011010	EP 1999-967639	19991222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002532729	T2	20021002	JP 2000-589188	19991222
US 6639078	B1	20031028	US 2001-868397	20010618
US 2004048316	A1	20040311	US 2003-637190	20030808

PRIORITY APPLN. INFO.: US 1998-135097P P 19981223
WO 1999-US30947 W 19991222
US 2001-868397 A1 20010618

OTHER SOURCE(S): MARPAT 133:68969

AB The present invention provides a method of identifying compds. for the treatment of diseases or disorders modulated by **farnesoid** X receptor (FXR), comprising the step of determining whether the compound interacts directly with FXR, wherein a compound that interacts directly with FXR is a compound for the treatment. A generic approach to assay development for nuclear receptors is presented, using purified ligand binding domains. The concept of generic assay development is extended to develop in vitro assays that detect ligand binding by monitoring ligand-induced changes in receptor heterodimerization. This approach is demonstrated using both scintillation proximity and homogeneous time-resolved fluorimetry (HTRF). Another aspect of the invention is a nuclear receptor peptide assay for identifying ligands. This assay utilizes fluorescence resonance energy transfer (FRET) and can be used to test whether putative ligands bind to FXR. The FRET assay is based upon the principle that ligands induce conformational changes in nuclear receptors that facilitate interactions with coactivator proteins required for transcriptional activation. Binding of the FXR nuclear receptor can result in the alteration of expression of various genes that FXR aids in regulating, including genes involved in lipid absorption and digestion in the small intestine and lipid homeostasis in liver. FXR often functions as a heterodimer with the RXR receptor. The inventive method includes using this technol. to affect bile acid and cholesterol homeostasis such that, ultimately, cholesterol and lipid levels can be modified and in treating diseases in a mammal, including human, in which regulation of bile acid, cholesterol and lipid levels is important. For example, GW4064 (prepared in a yield of 98%) was

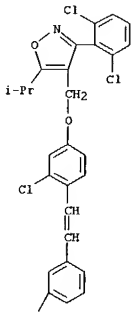
L7 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
given to Fischer rats at a dose of 30 mg/kg for 7 days. At the and of study, serum triglyceride levels were decreased by 26% compared to a vehicle-treated controls. Nearly 20 genes were identified in the intestine that were regulated >1.5-fold by GW4064. The expression of roughly half of these genes was decreased by GW4064 treatment. All of these down-regulated genes are involved in either lipid absorption or proteolysis, including lipases, proteases, and a colipase.

IT **278779-30-9P**, GW 4064
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(identification of nuclear receptor ligands for treatment of diseases affected by cholesterol, triglycerides and bile acid levels)

RN 278779-30-9 CAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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IT **278779-31-0P**, GW 4064 methyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

L7 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(prepn. of GW4064 as nuclear **farnesoid** X receptor ligand)

RN 278779-31-0 CAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]-, methyl ester (9CI) (CA INDEX NAME)

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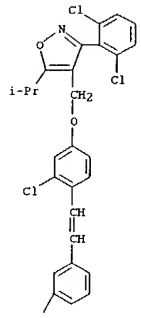

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-11.09	-11.09

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